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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Combinations of epinastine and sulfur containing amino acid as new pharmaceutical compositions for the treatment of skin diseases

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Combinations of epinastine and sulfur containing amino acid as new pharmaceutical compositions for the treatment of skin diseases

The present invention relates to new pharmaceutical compositions for the treatment of skin diseases related to allergic reactions. The composition comprises an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as a pharmacologically active compound and a sulfur containing amino acid as biologically active donor of a –S- or -SH group. The compositions also may comprise pharmaceutically acceptable additives.
The invention is of advantage in the treatment of pruritus (itching) derived from skin disease such as urticaria, eczema, and skin irritation.
Remarkably, the compositions described in the present invention are highly effective in the treatment of skin diseases associated with allergic reactions.

Background of the invention

In recent years, the incidence of developing skin diseases associated with allergic reactions has increased due to changes in diet, changes of the life style, air pollution, increased exposure to environmental chemicals from numerous environmental deterioration, stress in the social life and so on. Among these allergic reactions are urticaria, eczema, skin irritation, and dermatitis as well as skin diseases accompanying itching represented by pruritus, prurigo, psoriasis vulgaris etc.

Urticaria, a synonym of wheal, is a transient edema. The disease is characterized by a sudden onset of itchy sensation on skin, followed by developing well defined eruption swelling up like weal and growing into a size of nail plate to palm exacerbated by scratching. Although the symptoms disappear within a couple of minutes to hours and may not leave any skin disorder, episodes of development into eruption are likely to recur. Causes of urticaria may include autosensitization, sensitizations associated with difficult menstruation, pregnancy, foods, medicines and insect stings, abnormal responses to heat, cold, mechanical stimuli and light, remote responses to bacterial infections, gastrointestinal, hepatic, and renal disease, an endocrinopathic involvement, and psychological factors.

Eczema or dermatitis is the most major skin disease, characterized by inflammatory response on skin. Eczema and dermatitis are often referred altogether as eczematous dermatitis group. The diseases are often caused by pathological interactions caused by external stimuli (numbers of chemicals, fragrances, metals, detergents, medicines, plants, bacteria, insects, sunlight, heat, cold, dryness), internal abnormalities (local abnormalities such as perspiration, abnormal sebum secretion, abnormal keratosis, and systemic abnormalities such as atopic disposition, infection site, digestive disorder, renal dysfunction, endocrine disturbance), and bodily condition. Eczematous dermatitis group includes contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular eczema, autosensitization dermatitis, and lichen simplex chronicus Vidal.

Housewives' eczema, keratodermia tylodes palmaris progressiva, diaper dermatitis, and photocontact dermatitis are classified as atypical contact dermatitis. In addition, the group may include diffuse neurodermatitis, stasis dermatitis, infectious eczematoid dermatitis, and perioral dermatitis. Broadly, it may also include radiodermatitis, scald (burn), and frostbite.

Pruritus is a disease characterized by an onset of itchy sensation (itching) on apparently normal skin. Range of affected lesion divides pruritus into universal pruritus and localized pruritus. The disease is derived from a variety of causes, and often develops as a symptom of systemic disease.

Prurigo presents extreme itching and is papule or urticaria-like nodule that progress to chronic or recurrent disorder, and can be broadly classified into prurigo acuta including strophulus infantum, lichen urticatus, prurigo aestiralis, prurigo simplex acuta, prurigo subacuta such as prurigo simplex subacuta, and prurigo chronica including chronica multiformis, prurigo nodularis, prurigo Hebra, and prurigo simplex chronica. Mechanisms of the pathogenesis are unrevealed. Insect sting in prurigo acuta, and diabetes mellitus, hepatopathy, leukemia, Hodgkin's disease, visceral cancer, and polycythemia in prurigo chronica are thought of as causatives.

Psoriasis vulgaris is an inflammatory skin disease, and presents histological

characteristics of epidermal hyperplasia and inflammatory cellular infiltration. Eruption typically develops on head, extension side of extremities, and some parts of truncus which are in particular likely to come in contact with mechanical compression, in almost a half of which pruritus is observed. Immunological abnormalities may be concerned as a cause of disease.

It is emphasized that improvements on surroundings such as eliminating causative antigens is the most important treatment of these skin diseases, particularly for allergic skin disease. Nevertheless, as already reviewed, pathogenic causes are complicated, and therefore are fallible to be identified. Consequently, compositions combining antihistaminic compounds are of the frequent choice for treatments of these symptoms including itchy sensation caused from skin diseases.

Objective of the present invention

The present invention aims to provide compositions for the treatment of skin diseases that exert its significant utility to achieve effective improvements. In addition, the present invention intends to provide the compositions for treatment of skin diseases by employing highly effective pharmaceutical compounds for significant improvements on symptoms of skin diseases accompanying itching, particularly urticaria, eczema, skin fit, dermatitis, pruritus, eruption, and psoriasis vulgaris accompanying itchy sensation.

Description of the invention

The invention relates to a pharmaceutical compositions for the treatment of skin disease, whereas the composition comprises an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as pharmacologically active compound and one or more sulfur containing amino acid(s) or peptide(s).

Epinastine, (±) 3-amino-9, 13b-dihydro-1H-dibenz [c, f] imidazo [1,5-a] azepine, the hydrochloride thereof respectively, is a drug possessing H1-antihistaninic property. It primarily has been used to treat allergic reaction of the eyes and the nasal mucosa.

In the composition of the present invention Epinastine preferably is taken in the form

of a salt such as the hydrochloride, hydrobromide, oxalate, nitrate, sulfonate, fumarate, maleate, sulfate, and phosphate. The free base can be taken, too. Preferred is Epinastine-hydrochloride.

The amount of epinastine or a pharmacologically acceptable salt thereof depends on the application route.

In the case of oral application, the daily dosage in equivalent quantity of Epinastine-hydrochloride for an adult is between 2 and 20, preferably between 5 and 15 mg, and further more preferably between 7.5 and 12.5 mg. Preferably, this amount is given via one or more dosage units.

In the case of topical application the amount in equivalent quantity of Epinastine hydrochloride is between 1 and 50 mg per 1 g of composition, preferably between 2 and 30 mg per 1 g of composition, and further more preferably between 5 and 15 mg per 1 g of composition.

The sulfur containing amino acid(s) or peptide(s) shall act as biologically active donor(s) of a –S- or an -SH group. Sulfur containing amino acids are known to maintain or activate enzyme activities and thereby exert a biochemical reaction in which the SH group is involved.

In the context of the present invention the sulfur containing amino acid(s) or peptide(s) can be used as such or in the form of a pharmaceutically acceptable salt or as derivatives thereof.
Examples of these sulfur containing amino acid(s) or peptide(s) comprise cysteine, methionine, aminoethylsulfonic acid (taurine), glutathione, cystine, homocysteine, homocystine, cysteine sulfinic acid, lanthionine, mixtures thereof as well as their pharmaceutically acceptable salts or derivatives. It is also possible to use the mixed disulfides of any of the aforementioned compounds having a thiol-group. However, homogeneous disulfides are preferred among the disulfides. It is prefered to use one or more of these acids, particularly preferred are cysteine, methionine, taurine and glutathione as well as their pharmaceutically acceptable salts or derivatives.

The amount of the sulfur containing amino acid varies in dependency of the type, the combination choosen and the applicaiton route.

For oral use the daily dosage for an adult lies in the range of from 5 to 10000 mg, and for topical use it lies in the range of from 0.01 to 200 mg.

L-Cysteine is one of the preferred Sulfur containing acids to be used in the context of the present invention. For oral use the daily dosage for an adult lies normally in the range of from 5 to 1000 mg, preferably in the range of from 10 to 480 mg, and more preferably in the range of from 20 to 240 mg.

For topical use, the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

L-Methionine is used in oral formulations in daily dosages for an adult of between 0.5 and 5000 mg, preferably between 1 and 3000 mg, and more preferably between 2 and 1000 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Aminoethylsulfonic acid, known as taurine or 2-aminoethylsulfonic acid, is given in once per day dosages for an adult if applied orally which are between 5 and 10000 mg, preferably between 25 and 5000 mg, and more preferably between 30 and 3000 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Glutathione, γ-L-glutamyl-L-cysteinyl-glycine is given in once per day dosages for an adult if applied orally which are between 5 and 1000 mg, preferably between 25 and 600 mg, an more preferably between 50 and 300 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Dose adjustment of Epinastine and sulfur containing amino acid(s) or peptide(s) may reflect age, body weight, and manifesting symptoms.

The two essential components of the present invention epinastine and the sulfur containing amino acid(s) or peptide(s) can be combined together in one pharmaceutical preparation or the two components are formulated separately from each other in two pharmaceutical preparations and then given together or in close timely proximity, i.e. within 12 hours, preferably within 1 hour more preferably within 15 minutes and in particular preferred within 2 minutes.
Preferred are pharmaceutical compositions that contain both ingredients, i.e. the both ingredients are not separated.

The pharmaceutical compositions described in the present invention can be used in any oral form such as tablets, granules, subtle granules, powders, capsules, caplets, soft capsules, pills, suspensions, emulsions, oral solutions, syrups, dried syrups, chewable forms, forming tablets, drops, and orally disintegrable tablets, and in any topical form such as creams, ointments, gel ointments, suppositories, poultices, tapes, topical solutions, aerosols, lotions, and foams. In addition, preparation formed into microparticles such as microcapsule, nanocapsules, microspheres, nanospheres, liposomes may be also included in the aforementioned compositions.

Moreover, the properties of the inventive composition such as stability, release, continuance, disintegration, distinglation, dissolution, concealment of taste, improvement in usage etc. can be regulated by the addition of additives known in the art.

For example the pharmaceutically active substance can be dispensed in separate granules, multi-layer granules, multi-layer tablets or dry coated tablets, tablets of separated granules, microcapsules, etc. Coating preparations such as sugarcoated tablets, film coating tablets, coating granule, foaming pharmaceutical preparation can be used as well as chewable preparations, in the mouth dissolving preparations, matrix preparations, together with comminutions, solid solutions, etc. Sweetening agents, refrigerants, antioxidants or stabilizing agents, agents adjusting a certain pH-value can be added as well as the viscosity, the osmotic pressure or the salt concentration influencing agents. These methods can also be combined.

Optionally, also the following additives can be added: excipients, bases, binders, disintegrators, lubricants, superplasticizers, coating agents, sugar coating agents, plasticizers, antifoaming agents, polish, foaming agents, antistatic agents, desiccant, moisturizing agents, surfactant, solubilizer, buffer agents, resolvents, solubilizing agents, solvents, diluents, stabilizers, emulsifying agents, suspension, suspending agents, dispersing agents, isotonizing agents, aerosol propellant, adsorbents, reducing agents, antioxidant, backing, wetting agents, wet modifier, filler, extender, adhesives, viscous agent, softeners, pH modifiers, antiseptics, preservatives, sweetening agents, corrigent, refrigerative agents, flavoring agents, perfume, fragrance, coloring matters, and the like. Any of these additives may be used in the regular compositions methods, and do not impose any limitation to such composition methods.

Examples of these additives are explained in the Japanese Pharmaceutical Excipients Directory 2000 (Japan Pharmaceutical Excipients Council edit, Yakuji Nippo. Ltd. issue).

These preparations can be manufactured in the usual manner, f.e. by adding preparation additives to the pharmacologically active substance.

The compositions described in the present invention are explained by examples which follow. However, the present invention of the pharmaceutical compositions is

not limited to these examples.

Examples

Example 1

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 600 mg to prepare powder compositions.

Epinastine hydrochloride	10 g
L-cysteine	240 g
Corn starch	590 g
Lactose	940 g
Magnesium stearate	20 g

Example 2

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 120 mg each.

Epinastine hydrochloride	30 g
L-cysteine	720 g
Lactose	690 g
Microcrystalline cellulose	684 g
Light anhydrous silicic acid	18 g
Talc	9 g
Magnesium stearate	9 g

Example 3

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	20 g
L-methionine	400 g
Lactose	510 g

Microcrystalline cellulose	546 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g

Example 4

Oral solution

The following ingredients were dissolved in sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to get a total volume of 20 L. The resulted solution was transferred in portions of 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Aminoethylsulfonic acid	400 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 5

Syrup

The following ingredients were dissolved in sterile purified water, added with citric acid to adjust at pH 2.5, and then diluted with sterile purified water to prepare syrup at the total volume of 10 L.

Epinastine hydrochloride	20 g
Glutathione	200 g
Purified sucrose	4000 g
Sodium chloride	30 g
Sodium citrate	20 g

Citric acid	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 6

Sugarcoated tablet

The following ingredients were processed through a regular method to provide mixed particles, and the particle was compressed to form tablets at 240 mg each.

Epinastine hydrochloride	10 g
L-cysteine	240 g
Corn starch	648 g
Lactose	740 g
Microcrystalline cellulose	360 g
Hydroxypropylcellulose	90 g
Light anhydrous silicic acid	45 g
Talc	18 g
Magnesium stearate	9 g

Subsequently, the tablets were transferred into a coating pan, and coated using coating solution. The equal volume mixture of ethyl alcohol contained 5% weight/volume of hydroxypropylmetylcellulose and purified water to increase in weight/volume by 10 mg per one tablet. Next, 2% weight/volume of talc, 2% weight/volume of titanium oxide, 3% weight/volume of calcium carbonate, 1% weight/volume of powdered acacia, and aqueous solution containing 60% weight/volume of purified sucrose were used to coat tablets to give increase in weight/volume by 100 mg per one tablet. Finally, aqueous solution containing 60% weight/volume purified sucrose was used to coat tablets to give an increase in weight/volume by 100 mg per one tablet. Thus sugarcoated tablets were prepared.

Example 7

Granules

The following ingredients were prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1000 mg per one pack for

granules.

Epinastine hydrochloride	10 g
DL-methionine	1000 g
Calcium carboxymethylcellulose	240 g
Mannitol	1100 g
Corn starch	508 g
Tartaric acid	100 g
Aspartame	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

Example 8

Cream

The following ingredients were processed through a regular method to form a cream of a total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
L-cysteine	1.0 g
Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Methyl parahydroxybenzoate	0.2 g
Butyl parahydroxybenzoate	0.1 g
Purified water	Adequate amount

Claims

1. Pharmaceutical compositions for the treatment of skin diseases, comprising Epinastine or a pharmaceutically acceptable salt thereof as pharmacologically active compound and one or more sulfur containing amino acid(s) or peptide(s), preferably one or more sulfur containing amino acid(s).

2. Pharmaceutical compositions according to claim 1, characterised in that the composition is for oral use.

3. Pharmaceutical compositions according to claim 2, characterised in that the amount of Epinastine per day is between 2 and 20 mg in equivalent quantity to Epinastine hydrochloride.

4. Pharmaceutical compositions according to claim 1, characterised in that the composition is for topical use.

5. Pharmaceutical compositions according to claim 4, characterised in that the amount of Epinastine is between 1 and 50 mg per 1 g of the compositions in equivalent quantity to Epinastine hydrochloride.

6. Pharmaceutical compositions according to claim 2, characterised in that the amount of the sulfur containing amino acid(s) or peptide(s) per day is between 5 and 10000 mg.

7. Pharmaceutical compositions according to claim 4, characterised in that the amount of the sulfur containing amino acid(s) is between 0.01 and 200 mg per 1 g of the composition.

8. Pharmaceutical compositions according to any of the previous claims, characterised in that the sulfur containing amino acid(s) is (are) selected from

cysteine, methionine, aminoethylsulfonic acid, glutathione, cystine, homocysteine, homocystine, cysteine sulfinic acid, and/or lanthionine.

9. Pharmaceutical compositions according to any of the previous claims, characterised in that the composition comprises additives.

10. Use of a pharmaceutical compositions according to any of the previous claims, for the manufacture of a medicament for the treatment of skin diseases related to allergic reactions.

11. Use of a pharmaceutical composition comprising epinastine in combination with another pharmaceutical composition containing one or more sulfur containing amino acid(s) or peptide(s) for the manufacture of a medication for the treatment of skin diseases related to allergic reactions.

12. Use according claim 11 characterised in that the composition comprising epinastine and the composition containing one or more sulfur containing amino acid(s) or peptide(s) are applied in timely proximity.

13. Method for the treatment of skin diseases related to allergic reactions by applying pharmaceutical compositions according to any of the previous claims 1 to 9 to a patient.

14. Method for the treatment of skin diseases related to allergic reactions by applying a composition comprising epinastine and another composition containing one or more sulfur containing amino acid(s) or peptide(s) in timely proximity.

Abstract

The present invention relates to new pharmaceutical compositions for the treatment of skin disease. The composition comprises an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as a pharmacologically active compound and one or more sulfur containing amino acid(s) or peptide(s) as biologically active donor of a –S- or -SH group. The compositions also may comprise pharmaceutically acceptable additives.